8.5.12 Alphaviruses 821

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8.5.12 Alphaviruses 821 Kemerovo group Kemerovo group viruses have been isolated from ixodid and hyalomma ticks in Russia and Central Europe. They cause benign fe- brile illnesses and, occasionally, meningitis or encephalitis in spring and early summer when ticks are active. Rodents and birds are in- volved in the zoonotic cycle. The closely related Tribeč and Lipovník virus distributions range from Siberia to central Europe. Some healthy humans are sero- positive and so they may cause occasional fever or meningitis. The clinical features and epidemiology are similar to the flavivirus tick- borne encephalitis infection. Oklahoma tick fever is another Kemerovo virus rarely causing fe- brile illness in the United States of America. Changuinola There is a single report of human febrile illness with the orbivirus Changuinola in Panama. The virus has been isolated from phlebotomine flies and mammals in that area. Orungo Orungo virus is found mainly in West Africa but also in Uganda and the Central African Republic. Up to 75% of some human popu- lations are seropositive. The clinical effects are unknown, but fever, headache, myalgia, nausea, and diarrhoea occur in some people. There is no rash or jaundice. It is transmitted by Anopheles, Aedes, and other mosquitoes. Monkeys, sheep, and cattle may be infected. Lebombo This orbivirus was isolated from one febrile child in Nigeria. Lebombo is also found in mosquitoes and rodents. Seadornaviruses These viruses from Southeast Asia and Indonesia include Banna virus from China, which has been isolated from patients with en- cephalitis. In China, 20 new cases of Banna virus were identified in areas where Japanese encephalitis virus is endemic. These two en- cephalitis viruses share a common vector, Culex tritaeniorhynchus, and they may be clinically confused. Banna virus cases may be un- detected during a Japanese encephalitis virus outbreak. Prevention Tick-borne infections are prevented by avoiding, repelling with diethyltoluamide, and rapidly removing ticks. No vaccines are avail- able. Long-sleeved, tight-fitting clothing should be worn in the high-risk areas and the body should be checked for ticks at frequent intervals. The nucleoside analogue, 3′-fluoro-3′-deoxyadanosine, inhibits replication in vitro. FURTHER READING Attoui H, et al. (2005). Coltiviruses and seadornaviruses in North America, Europe, and Asia. Emerg Infect Dis, 11, 1673–9. Hubálek Z, Rudolf I (2012). Tick-borne viruses in Europe. Parasitol Res, 111, 9–36. Libikova H, et al. (1978). Orbiviruses of the Kemerovo complex and neurological diseases. Med Microbiol Immunol, 166, 255–63. Liu H, et al. (2010). Banna virus, China, 1987–2007. Emerg Infect Dis, 16, 514–7. McGinley-Smith DE, Tsao SS (2003). Dermatoses from ticks. J Am Acad Dermatol, 49, 363–92. Romero JR, Simonsen KA (2008). Powassan encephalitis and Colorado tick fever. Infect Dis Clin North Am, 22, 545–59. Silva SP, et al. (2014). Genetic and biological characterization of selected Changuinola viruses (Reoviridae, Orbivirus) from Brazil. J Gen Virol, 95, 2251–9. Yendell SJ, Fischer M, Staples JE (2015). Colorado tick fever in the United States, 2002–2012. Vector Borne Zoonotic Dis, 5, 311–6. 8.5.12 Alphaviruses Ann M. Powers, E.E. Ooi, L.R. Petersen, and D.J. Gubler

ESSENTIALS There are 31 registered alphaviruses belonging to the family Togaviridae, 16 of which are known to cause human infection. They are RNA viruses with global geographical distribution and complex transmission cycles, usually between wild or domestic animals and one or more mosquito species; humans are infected by mosquito bites and are often inci- dental hosts that do not contribute to the maintenance of the virus. They cause a spectrum of clinical manifestations ranging from non- specific febrile illness to chronic arthralgia to acute encephalitis and death. Diagnosis of infection is made by several methods including (1) serologically by detection of IgM and/or IgG antibodies, (2) virus isolation, (3) molecularly using reverse transcription–polymerase chain reaction, or (4) by immunohistochemistry on tissue samples. Old World alphaviruses, including chikungunya, Ross River, Sindbis, Barmah Forest, Mayaro, and o'nyong-nyong, generally have mammals as their natural vertebrate host and cause acute febrile illness charac- terized by rash and arthritis. Clinical management is symptomatic; pre- vention and control is by reducing vector mosquito populations and by avoiding mosquito bites. Several efforts to develop vaccines for chikun- gunya and Ross River viruses are in progress and are at different stages of development. The New World alphaviruses, eastern and western equine enceph- alitis viruses, generally have birds as their natural vertebrate hosts, while the Venezuelan equine encephalitis complex viruses have rodents as their natural hosts. About 2% of adults infected with eastern equine enceph- alitis virus (less for other viruses) develop encephalitis which can be fatal, with permanent neurological sequelae in many survivors. As with the Old World alphaviruses, management is symptomatic; prevention and control is by reducing vector mosquito populations and by avoiding mosquito bites. Various vaccines have been used in laboratory workers and others at high risk of exposure. New generation vaccines are in development.

822 section 8 Infectious diseases Introduction The genus Alphavirus of the family Togaviridae is comprised of 31 registered viruses, 16 of which are known to cause human in- fection (Table 8.5.12.1). Alphaviruses are lipid-enveloped virions with a diameter of 60–70 nm whose genome is a molecule of single- stranded, positive-sense RNA approximately 12 000 nucleotides in length. Most alphaviruses are maintained in nature in complex trans- mission cycles between wild or domestic animals and one or more mosquito species. Humans are infected when the infected mosquito bites them and transmits the virus via their saliva. Patients develop high viraemias with some alphaviruses and this may contribute to the transmission cycle by infecting mosquitoes. The epidemiology and geographical distribution of the alphaviruses depend on several Table 8.5.12.1 Known disease associations of alphaviruses Virus Geographical distribution Disease in humans Outbreaks Other features Aura South America No Barmah Forest Australia SFI, arthropathy Yes Clinically similar to Ross River virus infection Bebaru Malaysia No Laboratory infection only Cabassou French Guiana No Chikungunya Africa, Asia, South America, Central America, Caribbean, South Pacific SFI, arthropathy Yes Large outbreaks in urban settings Eastern equine encephalitis North America on Atlantic and Gulf Coasts, Caribbean SFI, encephalitis Yes Isolated cases or small outbreaks occur mainly in North America Eilat Israel Insect only alphavirus Everglades Florida SFI, encephalitis No Member of the Venezuelan equine encephalitis antigenic complex Fort Morgan Colorado, California, Nebraska, Oklahoma No Getah Asia SFI No Highlands J North America SFI No Madariaga South America, Central America SFI Formerly South American variants of eastern equine encephalitis virus Mayaro South America, Caribbean SFI, arthropathy Yes Middelburg South, West, and Central Africa No Mosso das Pedras Brazil, Argentina No Member of the Venezuelan equine encephalitis antigenic complex Mucambo Trinidad, South America SFI No Member of the Venezuelan equine encephalitis antigenic complex Ndumu Africa No Onyong-nyong East and West

Africa, Zimbabwe SFI, arthropathy Yes Igbo Ora virus is a variant of onyong-nyong Pixuna Brazil, Argentina SFI No Rio Negro Argentina No Ross River Australia, South Pacific SFI, arthropathy Yes Periodic epidemics in South Pacific Salmon Pancreas disease North Atlantic No Semliki Forest Sub-Saharan Africa SFI, encephalitis No Sindbis Africa, East Mediterranean, South and Southeast Asia, Australia, Europe SFI, arthropathy Yes Subtypes includes Babanki, Kyzylagach, Ockelbo Southern elephant seal Antarctica No Tonate French Guiana SFI, encephalitis No Member of the Venezuelan equine encephalitis antigenic complex Trocara South America No Una South America, Trinidad No Venezuelan equine encephalitis Northern South America, Central America, Mexico SFI, encephalitis Yes Epidemics are caused by epizootic virus strains (Subtypes IAB and IC) Western equine encephalitis North and South America SFI, encephalitis Yes Human disease rare outside of North America and Brazil; Whataroa New Zealand, Australia No SFI, systemic febrile illness. Adapted from Griffin D (2007). Alphaviruses. In: Knipe DM, Howley PM (eds) Fields virology, 5th edition, vol. 1, pp. 1023–67. Lippincott Williams & Wilkins, Philadelphia.

8.5.12 Alphaviruses 823 factors including the presence of suitable amplifying hosts, the pres- ence and feeding behaviour of suitable arthropod vectors, and the frequency of exposure of nonimmune reservoir hosts and humans to infected vectors. Alphavirus infections are not directly communicable between humans. Many alphavirus infections in humans are asymptomatic, but alphaviruses can cause a spectrum of clinical illness ran- ging from nonspecific febrile illness, often with rash, myalgia, or arthralgia, to frank encephalitis, haemorrhage, and death. They cause two main clinical syndromes: Old World alphaviruses generally cause illness characterized by rash and arthritis while New World alphaviruses are generally associated with neuroinvasive disease. No specific therapy is available. Vaccines for some alphaviruses are used in animals, although none have been licensed for humans. Laboratory diagnosis Alphavirus infections are diagnosed serologically by detection of IgM and/or IgG antibodies. All alphaviruses have some common antigenic determinants that may result in cross-reactions in immunodiagnostic tests. Neutralization tests are typically confirma- tory for serological diagnosis in areas where multiple alphaviruses are endemic/enzootic. Isolation of virus from acute-phase serum is possible with some alphaviruses, but they are seldom recovered from the central nervous system, including cerebrospinal fluid, except from fatal cases. Virological diagnosis can also be made using polymerase chain reaction and immunohistochemistry on tissue samples. Alphaviruses associated with arthritis and rash Chikungunya Aetiology and epidemiology Chikungunya virus has a nearly global distribution and is trans- mitted primarily by day-biting Aedes sp. mosquitoes. The primary vertebrate reservoir hosts remain to be conclusively determined, although nonhuman primates such as monkeys and baboons are likely candidates in sylvatic environments in Africa. In urban surroundings, the virus is transmitted between humans by Aedes aegypti and Ae albopictus mosquitoes. Explosive urban epidemics occur during the rainy season in long endemic areas and year- round in previously chikungunya-free areas. Since 2004, chi- kungunya virus spread extensively, beginning with outbreaks on the East Coast of Africa then moving to the islands of the Indian Ocean, India, and Southeast Asia. This epidemic was exacerbated by a new variant of the virus containing a single amino acid mu- tation in the envelope protein. This mutation increased infectivity for Ae albopictus, a mosquito that has spread throughout the tropics and subtropics and has a wider distribution in urban, semiurban, and rural habitats than Ae aegypti, which favours urban environ- ments. In 2007, it reached a subtropical country (Italy) for the first time. The activity in Italy involved local transmission by Ae albopic- tus mosquitoes resulting in 205 cases and one death. The outbreaks continued to spread, finally reaching the Americas (Caribbean) in 2013. However, the outbreaks in

the Americas were not an ex- tension of the Indian Ocean outbreaks but rather an independent introduction of the Asian genotype into the Western Hemisphere. Within 1 year, chikungunya virus had spread to 44 countries in the Americas and caused an estimated 1.1 million cases. Serological surveys following outbreaks have shown antibody prevalences gen- erally ranging from 30% to 70%. Clinical characteristics ‘Chikungunya’ means ‘that which bends up’ in Makonde, an East African language, and refers to the crippling arthralgia that char- acterizes the disease. After an incubation period of 2–3 days (range 1–12 days), there is sudden and high (>39°C) fever and severe arthralgia. Arthralgias are polyarticular, with the knees, ankles, elbows, and small joints of the hands and feet most commonly affected. A useful sign is pain on squeezing the wrists (tenosyno- vitis). Headache, injected pharynx, gastrointestinal symptoms, and myalgias can be frequent during the acute illness. Rashes, typically on the trunk and limbs, occur in about one-half of the patients, usually during the second to fifth day of illness. They are variable in appearance: papular or maculopapular erythemas (blanching as in dengue), vesicular, bullous, dyshidrotic, keratolytic, pur- puric and hyperpigmented associated with facial oedema, ery- thema nodosum, and aphthous ulcers. Arthralgia might last several months and is associated with effusions and bursitis; a few patients have symptoms 5 years after infection. Haemorrhage, meningo-encephalitis, Guillain–Barré polyradiculopathy, myocarditis, and hepatic and renal complications are uncommon but may be fatal. Rheumatological manifestations are less frequent in children. Conjunctival suffusion and cervical or generalized lymphadenop- athy can occur. Serological surveys suggest that asymptomatic in- fections can occur but typically in less than 20% of those infected. Neonatal infection has occurred from mothers ill shortly before or at the time of delivery resulting in more severe manifestations in the newborns. Diagnosis Leukopenia and elevation of liver and muscle enzymes are common early in infection. Detection of viral RNA by reverse transcription– polymerase chain reaction (RT-PCR) is particularly useful for diagnosis given the high titres and long duration of viremia. Haemagglutinin inhibition and IgM antibodies will be present in nearly all patients by the seventh day of illness. IgM antibodies detectable in serum by IgM antibody capture enzyme-linked im- munosorbent assay (MAC-ELISA) may persist for 6 months after infection. Virus isolation and RT-PCR both provide confirmed diagnosis. Prevention, control, and treatment Prevention and control can only be achieved by reducing vector mosquito populations in the large urban centres of the tropics and by avoiding mosquito bites. The American military devel- oped an investigational vaccine, but it is not licensed for general use. Several new vaccines using a variety of approaches including subunit vaccines, chimeric vaccine, virus-like particle vaccines, and DNA vaccines are all in late stage development. There is no specific treatment. Anti-inflammatory drugs might relieve arthralgia and a range of potential therapeutic agents are being evaluated.

824 section 8 Infectious diseases Ross River virus Aetiology and epidemiology This virus causes ‘epidemic polyarthritis’ in Australia, south-western Pacific islands, and Fiji. Aedes vigilax and Culex annulirostris are im- portant vectors in Australia and Ae scutellaris complex mosquitoes in some south Pacific islands, although the virus has been isolated from more than 30 mosquito species. An epidemic in various Pacific islands in 1979 to 1980 affected more than 50 000 people with up to 60% of the population affected on some islands. An average of 5000 cases is reported annually from Australia. Explosive outbreaks and viraemias in humans implicate virus transmission from human to human by certain mosquitoes. Outbreaks tend to be associated with periods of increased rainfall. Camping is a significant risk factor in tropical Australia; however, recent outbreaks have reached the borders of major coastal urban areas where human expansion has brought populations

closer to vector habitats. Clinical characteristics The incubation period ranges from 2 to 21 days (7–9 days on average). The illness begins suddenly with fever and arthralgias predomin- antly in the ankles, wrists, knees, fingers, and feet. A maculopapular rash occurs in about one-half of patients within 2 days of onset and is most prominent on the trunk and limbs, but can cover the entire body; the rash may progress to small vesicles. Myalgias, headache, anorexia, nausea, and tenosynovitis are common, but the tempera- ture is only slightly elevated. Arthralgia generally resolves within 3 to 6 months. Symptomatic infection is rare in children. Diagnosis Isolation of virus from serum is possible for the first few days of illness. IgM antibodies will be detected by MAC-ELISA within 5–10 days of onset. Complement fixation, haemagglutinin inhib- ition, and neutralization tests may be useful, particularly when paired serum samples are available. Virus isolation and PCR are confirmatory. Prevention, control, and treatment Avoidance of mosquito bites and peridomestic mosquito control can effectively reduce the risk of infection. No specific treatment is available. Nonsteroidal anti-inflammatory drugs might relieve symp- toms. One study suggested that corticosteroids might hasten recovery. Vaccines against this virus are in preclinical stages of development. Sindbis Aetiology and epidemiology Sindbis virus is widely distributed in Africa, India, tropical Asia, Australia, and Europe. However, clinical disease is reported only in geographically restricted areas where specific variants are de- scribed. In Europe, the main vectors to humans are late summer, ornithophilic mosquitoes of the genera Culex and Culiseta. High antibody prevalences in regions of Africa suggest that human ex- posure is common. Several outbreaks have been noted since the ori- ginal identification of the virus in 1952. Clinical characteristics In northern Europe, symptomatic disease is recognized from Sweden (Ockelbo disease), through Finland (Pogosta disease), to the former Karelian Autonomous Soviet Socialist Republic (Karelian fever). The clinical features include mild fever, rash, arthralgia, my- algia, malaise, headache, and pruritus. The maculopapular rash progresses from trunk to extremities and vesicles can occur on the palms and soles. Ankle, finger, wrist, and knee joints are most com-monly affected. While disease symptoms are typically mild, prom- inent rheumatic symptoms, sometimes persisting for several years, have been noted in Europe and South Africa. Diagnosis Haemagglutinin inhibition and IgM antibodies will be present in nearly all patients by the eighth day of illness. IgM antibodies de- tectable in serum by MAC-ELISA may persist for 6 months after infection. Virus can be infrequently detected by culture or RT-PCR from blood or skin lesions. Prevention, control, and treatment Avoidance of mosquito bites can reduce the risk of infection. No specific treatment is available. Barmah Forest virus Since its first recognition as a cause of human disease in 1988, the geographical distribution of Barmah Forest virus has expanded re- cently in Australia. It causes sporadic disease and epidemics, with up to 300 serologically confirmed cases. The disease resembles that of Ross River virus infection, although the rash tends to be more florid and true arthritis is less common. The illness is prolonged in some patients. Little is known about the ecology of Barmah Forest virus, although outbreaks have coincided with Ross River virus outbreaks and the virus has been identified in the same mosquito species. Mayaro virus Mayaro virus has been isolated from humans, wild vertebrate reser- voir species, and Haemogogus sp. mosquitoes, the principal vectors, in Trinidad, Colombia, Brazil, Suriname, Guyana, French Guiana, Peru, Bolivia, Venezuela, and most recently in Haiti. Seroprevalence is high in human populations in many forested areas of South America. The clinical presentation resembles chikungunya, onyong-nyong, Ross River, Barmah Forest, and Sindbis virus infections. In an outbreak in Pará, Brazil, after an incubation period of about a week, fever, chills, headache, arthralgia, myalgia, and lymphadenopathy developed and persisted for 2–5 days. Arthralgia was almost uni- versal and could last for months. Small joints in the extremities were principally involved. It was accompanied

by joint oedema in 20% of cases, causing severe temporary disability. Maculo- or micropapular rashes appeared on the fifth day and lasted for 3–4 days in two-thirds of the cases, more in children (Fig. 8.5.12.1). All patients had leuco- penia and a minority had mild thrombocytopenia and albuminuria. Viraemias as high as 5.0 log/ml suggested that humans might be amplifying hosts for this virus. In other outbreaks, eye pain, diar- rhoea, and vomiting were additional features. Onyong-nyong virus From 1959 to 1962, this virus caused an epidemic in Uganda, Kenya, Tanzania, and Malawi involving approximately 2 million people. The virus was also isolated in 1978 from Anopheles funestus mosqui- toes in Kenya after a long period of no apparent onyong-nyong virus activity. In 1996–1997, an outbreak occurred in Uganda. However,

 in West Africa, variants known as Igbo Ora have been found but have not been associated with large outbreaks. In 2003, a small out- break occurred among refugees in the Côte d’Ivoire and a human infection was confirmed in Chad in 2004. Onyong-nyong is closely related to chikungunya and produces a similar illness, although fever is less pronounced and cervical lymphadenopathy is very common. An funestus and An gambiae transmit the virus; onyong-nyong virus is the only alphavirus to utilize anopheline vectors. Alphaviruses associated with neuroinvasive disease Eastern equine encephalitis Aetiology and epidemiology The virus is widely distributed throughout eastern North America and the Gulf Coast. In North America, it is maintained in a bird– mosquito cycle in hardwood swamps in coastal areas from the Great Lakes and southeastern Canada to the Gulf Coast. Recent studies have suggested that snakes may serve as overwintering reservoirs in southern states. In the United States of America human infections are usually sporadic, and small outbreaks occur each summer mostly along the Atlantic and Gulf Coasts; outbreaks of equine disease are common in Florida. In recent years, 1–21 cases have been reported annually. In North America, wild birds and Culiseta melanura mosquitoes maintain the virus in hardwood swamps, but a variety of mosquito species act as bridge vectors to humans and domestic animals. The newly named Madariaga virus was formerly known as South American eastern equine encephalitis virus. Madariaga virus is less associated with human or equine disease and is likely main- tained in a transmission cycle distinct from eastern equine enceph- alitis virus in North America. Clinical characteristics Most infections are inapparent. The incubation period exceeds 1 week with a prodromic period that lasts up to 11 days before high fever and neurologic symptoms appear. About 2% of infected adults and 6% of children develop encephalitis. Eastern equine encephalitis is the most severe of the arboviral encephalitides, with a mortality of 30– 70% in those that develop encephalitis. Symptoms and signs include dizziness, decreasing level of consciousness, tremors, seizures, and focal neurological signs. Death can occur within 3–5 days of onset of neurological symptoms. Lifelong neurological sequelae are common in nonfatal encephalitis and include convulsions, paralysis, and cog- nitive impairment. Illness due to eastern equine encephalitis in South America (Madariaga virus infection) appears to be less severe. Diagnosis Cerebrospinal fluid pressure can be raised, protein levels are increased, sugar is normal, and pleocytosis exists (up to 2000 cells/mm3). IgM antibodies are readily detected in serum or cerebrospinal fluid by ELISA. Paired serum samples can be tested by haemagglutinin inhib- ition, ELISA, or neutralization tests. Horse or pheasant deaths and the proximity to swamps provide clues to the diagnosis. Prevention, control, and treatment Prevention depends on the avoidance of mosquito bites and mos- quito control in suburban areas. Inactivated vaccines have been used successfully in horses, and an investigational inactivated vaccine has been used experimentally in laboratory workers and others at high risk of exposure. No specific treatment is available. Venezuelan equine encephalitis antigenic complex Aetiology and epidemiology Six subtypes (I–VI)

within the Venezuelan equine encephalitis anti- genic complex have been identified. Five antigenic variants exist within subtype I (IAB, IC, ID, IE, IF). These subtypes and variants are classified as epizootic or enzootic, based on their apparent viru- lence and epidemiology. Epizootic variants of subtype I (IAB and IC) cause equine epizootics and are associated with more severe human disease. Only subtypes IAB, IC, ID, and IE are classified as Venezuelan equine encephalitis virus; all other subtypes are distinct viral species. Enzootic strains (ID, IE, IF (Mosso das Pedras virus), II (Everglades virus), III (Mucambo virus [A, B, D], Tonate virus [B]), IV (Pixuna virus), V (Cabassou virus), VI (Rio Negro virus)) do not cause epizootics in horses, but can produce sporadic disease in humans. Large epizootics (IAB and IC) have occurred in equines in northern countries of South America and Central America, sometimes reaching the United States of America. In 1969–1972, a massive epizootic extending from Ecuador to Texas killed more than 200 000 horses and caused several thousand human infections. In 1995, a large epizootic, which began in Venezuela and spread to (a) (b) Fig. 8.5.12.1 Mayaro virus infection acquired in the Peruvian Amazon, showing maculopapular rash that first appeared on the palms of the hands on the fifth day spreading first to arms, knees, and then to entire body and lasting 3 days, accompanied by arthralgia and swelling of the fingers and feet, later affecting the knees. Rash is similar in appearance to that seen in chikungunya, onyong-nyong, Sindbis, and Ross River cases. Courtesy of Dr Celie Manuel.

826 section 8 Infectious diseases Colombia, affected thousands of horses, and caused approximately 90 000 human infections. Epizootic strains are carried by a wide var- iety of mosquitoes including Aedes, Mansonia, and Psorophora spp. Horses are the principal amplifying hosts during epizootics but are not amplifying hosts for enzootic transmission. Enzootic strains are maintained in a cycle involving Culex (Melanoconion) mosquitoes and rodents. Subtype IE Venezuelan equine encephalitis virus has caused some small equine outbreaks in Mexico, but it is still con- sidered an enzootic subtype. Clinical characteristics (epizootic virus infections) After an incubation period of 1–6 days, there is a brief febrile illness of sudden onset characterized by malaise, nausea, or vomiting, head- ache, and myalgia. Acute symptoms last 2–5 days, and generalized asthenia up to 3 weeks. Clinically, Venezuelan equine encephalitis can be indistinguishable from dengue or other arboviral diseases. Among those with clinical illness, less than 0.5% of adults and less than 4% of children develop encephalitis. Nausea and vomiting, nu- chal rigidity, ataxia, convulsions, paralysis, and death may occur. Long-term sequelae following encephalitis are uncommon. Diagnosis (epizootic virus infections) A marked leukopenia is universal, often accompanied by neutropenia and thrombocytopenia, with moderate lymphocytosis in the cerebro- spinal fluid. Virus can be detected by isolation or by RT-PCR from serum or throat swab within the first few days of illness. Paired sera can be tested by haemagglutinin inhibition and neutralizing tests. Specific IgM can be detected by MAC-ELISA in the second week of illness. Prevention, control, and treatment Equine immunization has been effective in controlling epizootic disease. Venezuelan equine encephalitis is highly infectious by the aerosol route and many laboratory infections have occurred. Investigational live attenuated and inactivated vaccines have been used in laboratory workers. People in affected areas should avoid mosquito bites. No specific treatment is available. Western equine encephalitis Aetiology and epidemiology Western equine encephalitis virus is found in North and South America, but human disease is rare outside North America and Brazil. Previously, summer outbreaks tended to occur with flooding, which increases breeding of Culex mosquitoes (particularly Culex tarsalis in the western United States of America). Large outbreaks of western equine encephalitis in humans and horses occurred in the western United States of America in the 1950s and 1960s; however, a declining horse population, equine vaccination, viral mutations, and improved vector control have reduced the reported number of

human cases to zero in recent years. Clinical characteristics The ratio of apparent to inapparent infection in adults is less than 1 in 1000; however, this ratio increases to 1:1 in infants under 1 year of age. Following an incubation period of about 7 days, headache, vomiting, stiff neck, and backache are typical; restlessness and irrit- ability are seen in children. Weakness and hyporeflexia are common. Convulsions occur in 90% of affected infants and 40% of affected children between 1 and 4 years, but are rare in adults. Recovery in 5–10 days is common, but convalescence may be protracted. Although rare in adults and older children (<1%), sequelae are common in newborns, with one-half of those with encephalitis being left with convulsions and/or severe motor or intellectual deficits. Congenital infection during the third trimester resulting in encephalitis in the infant has been described. The overall case fatality rate is 3–7%. Diagnosis Clinical laboratory findings in western equine encephalitis are often unremarkable. IgM antibodies are readily detected in serum by ELISA. Paired sera can be tested by haemagglutinin inhibition, IgG ELISA, or neutralization tests for a rise in titre. Virus can occasion- ally be isolated from serum or cerebrospinal fluid but odds of isola- tion decrease with the onset of neurologic symptoms. Isolation from the brain post-mortem is common. Prevention, control, and treatment Prevention of western equine encephalitis relies on mosquito con- trol and the avoidance of mosquito bites. A licensed vaccine is avail- able for horses. An investigational inactivated vaccine has been used for laboratory staff and others at high risk of exposure. No specific treatment is available. FURTHER READING Aichinger G, et al. (2011). Safety and immunogenicity of an inacti- vated whole virus Vero cell-derived Ross River vaccine: a random- ized trial. Vaccine, 29, 9376–84. Centers for Disease Control and Prevention (2006). Eastern equine en- cephalitis: New Hampshire and Massachusetts, August–September 2005. MMWR Morb Mortal Wkly Rep, 55, 697–700. Griffin D (2007). Alphaviruses. In: Knipe DM, Howley PM (eds) Fields virology, 5th edition, Vol. 1, pp. 1023–67. Lippincott Williams & Wilkins, Philadelphia, PA. Halsey ES, et al. (2013). Mayaro virus infection, Amazon Basin region, Peru, 2010–2013. Emerg Infect Dis, 19, 1839–42. Kiwanuka N, et al. (1999). O'nyong-nyong fever in South-Central Uganda, 1996–1997: clinical features and validation of a clinical case definition for surveillance purposes. Clin Infect Dis, 29, 1243–50. Laine M, et al. (2004). Sindbis virus and other alphaviruses as cause of human arthritic disease. J Int Med, 256, 457–71. Petersen LP, Powers AM (2016). Chikungunya: epidemiology. F1000Research, 5(F1000 Faculty Rev), 82. Pialoux G, et al. (2007). Chikungunya, an epidemic arbovirosis. Lancet Infect Dis, 7, 319–27. Powers AM (2011). Genomic evolution and phenotypic distinctions of Chikungunya viruses causing the Indian Ocean outbreak. Exp Biol Med (Maywood), 236, 909–14. Powers AM (2018). Vaccine and Therapeutic Options to Control Chikungunya Virus. Clin Microbiol Rev, 13, e00104–16. Schwartz O, Albert ML (2010). Biology and pathogenesis of chikun- gunya virus. Nat Rev Microbiol, 8, 491–500. Suhrbier A, Jaffar-Bandjee MC, Gasque P (2012). Arthritogenic alphaviruses—an overview. Nat Rev Rheumatol, 8, 420–9. Tesh RB, et al. (1999). Mayaro virus disease: an emerging mosquito- borne zoonosis in tropical South America. Clin Infect Dis, 28, 67–73. Weaver SC, et al. (2004). Venezuelan equine encephalitis. Annu Rev Entomol, 49, 141–74. Zacks MA, Paessler S. (2010). Encephalitic alphaviruses. Vet Microbiol, 140, 281–6.

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